REMARKS

Claims 1-63 were pending in the present application. Claims 3, 4, 7, 8, 18-20, 23-24, 26, 29-34, 36-40, 44, 45 and 52-63 were previously withdrawn from consideration as drawn to a non-elected invention. By virtue of this response, claims 23 and 24 have been amended for clarity. Accordingly, claims 1, 2, 5, 6, 9-17, 21, 22, 25, 27, 28, 35, 41, 43 and 46-51 are currently under consideration. Amendment and cancellation of certain claims is not to be construed as a dedication to the public of any subject matter of the claims as previously presented.

Applicants request rejoinder of methods claims to the extent they incorporate all the limitations of allowed composition claims. In re Ochiai.

Attached hereto is a marked-up version of the changes made to the claims by the current amendment. The attached pages are captioned "**VERSION WITH MARKINGS TO SHOW CHANGES MADE**".

Concerning the Sequence Listing

Applicants acknowledge that the CRF and paper sequence listing have been entered.

Concerning the Information Disclosure Statements

The Examiner indicated that the initialed and dated copy of Applicant's IDS form 1449, Paper Nos. 3 and 10, were attached to the Office Action (Paper No. 14). Please be advised that these copies were not attached to the Office Action as indicated. Applicants thank the Examiner for sending via facsimile these initialed copies.

Concerning the drawings

Applicants acknowledge that correction of Figure 8 is required. Applicants submit concurrently herewith a corrected Figure 8 that Applicants believe is in compliance with 37 CFR 1.84(I) (p).

Concerning rejection of claims under 35 U.S.C. § 112, first paragraph

Claims 1, 2, 12, 13, 14, 21, 22, 25, 27, 28, 35, 43, 50 and 51 are rejected under 35 U.S.C. 112, first paragraph, allegedly because the specification, while being enabling for changing the viral tropism of a bovine adenovirus to infect a human cell line by substituting the human adenovirus fiber protein, does not reasonably provide enablement for altering the viral tropism by changing only the hexon or penton protein.

Applicants traverse this rejection.

Applicants submit that pursuant to M.P.E.P. Section 2164.04, the Examiner has the initial burden to establish a reasonable basis to question the enablement provided for the claimed invention. The Examiner must provide a reasonable explanation as to why the scope of the protection provided by the claims is not adequately enabled by the disclosure. Applicants submit that the Examiner has not presented a reasonable explanation or technical evidence to support this enablement rejection and therefore has not established a *prima facie* case of nonenablement. Assuming *arguendo* that the Examiner has established a *prima facie* case of non enablement, which Applicants don't concede, Applicants submit that the specification teaches how to make and use the claimed invention, throughout its scope without undue experimentation.

A. In the Restriction Requirement dated September 6, 2002, Applicants were required to elect an invention from among hexon, penton and fiber if certain groups were elected. Applicants elected Group I, "fiber" for prosecution (with traverse). In making the Section 112 rejection of claims, the Examiner alleges that the specification does not reasonably provide enablement for altering the viral tropism by changing only the hexon or penton protein. First of all, Applicants request clarity from the Examiner regarding consideration of the withdrawn inventions, hexon and penton. According to 37 C.F.R. 1.142(b), inventions not elected are withdrawn from further consideration by the Examiner by the election, subject to reinstatement in the event the requirement for restriction is withdrawn or overruled. Applicants request clarity from the Examiner if she is withdrawing the requirement for the further election, and is therefore

considering fiber, hexon and penton, or has the Examiner deemed the invention, fiber, to be in full compliance with Section 112, first paragraph and is now considering hexon and penton.

The Examiner states that the specification is enabling for changing the viral tropism of a bovine adenovirus to infect a human cell line by substituting the human adenovirus fiber protein and alleges that the specification is not enabled for altering the viral tropism by changing only the hexon or penton protein. Applicants point out that the claims do not recite "altering the viral tropism by changing only the hexon or penton protein". Independent claim 1 recites "A bovine adenovirus vector comprising a modification in a polynucleotide encoding a capsid protein, or fragment thereof, wherein said capsid protein, or fragment thereof, is associated with tropism and wherein said modification is associated with altered tropism". Independent claim 35 recites "A recombinant bovine adenovirus comprising a modification in a polynucleotide encoding a capsid protein, or fragment thereof, wherein said capsid protein, or fragment thereof, is associated with tropism and wherein said modification is associated with altered tropism." It is well established that an inventor need not necessarily disclose how to make each and every embodiment encompassed by the claim.

Applicants demonstrate in an illustrative embodiment that a bovine adenovirus vector comprising a modification in a polynucleotide encoding a fiber protein knob region is associated with altered tropism. The specification at page 42, Example 3 discloses that the bovine adenovirus BAV600, that comprises nucleic acid that encodes a HAV-5 fiber knob region fused to the BAV-3 tail and shaft, is able to transduce human HeLa cells, Hep-2 cells, 293 cells and A549 cells whereas there was a complete absence of viral replication of wild-type BAV-3 in these same cells.

Additional adenovirus capsid proteins are disclosed in the present specification, see Figures 12-16 and page 25, lines 3-13, and were known in the art at the time of filing of the present patent application. As disclosed in Fields Virology (Third Edition, ed. Fields et al., pub. Lippincott-Raven, page 2115) capsid proteins include hexon, penton and fiber proteins along with proteins IIIa, VI, VIII, and IX. See also Zheng et al. (1994, *Virus Research* 31:163-186)

which disclose the nucleotide sequence of bovine adenovirus capsid protein IX; Mittal et al. (1992, *J. Gen. Virol.* 73:3295-3300) which disclose the sequence of bovine adenovirus capsid protein VIII and fiber genes; Reddy et al. (1998, *J. of Virol.* 72: 1394) which disclose the transcriptional and translational features of BAV-3; and Reddy et al. (1999, *Virology*, 253:299-308) which disclose characterization of the early region 1 and pIX of BAV-3. All references are submitted in the Supplemental Information Disclosure Statement (IDS) filed concurrently herewith or were previously submitted in an IDS of record. The present invention encompasses modifications in capsid proteins including hexon, penton and fiber proteins, as well as modifications in capsid proteins IIIa, VI, VIII and IX that are associated with altered tropism.

Applicants attach hereto pursuant to 37 C.F.R. § 1.132, a Declaration by Dr. Suresh K. Tikoo ("Tikoo Declaration"), an expert in molecular biology and adenovirus technology and inventor of the claimed subject matter. As disclosed in the Tikoo Declaration, a modification in bovine adenovirus capsid protein IX is associated with altered tropism. As described in the Tikoo Declaration at paragraph 5, a replication-competent bovine adenovirus-3 (BAV-3) vector having a modified capsid pIX gene comprising nucleic acid encoding an Arg-Gly-Asp (RGD) peptide, designated pBAV950, was constructed. As described in the Tikoo Declaration at paragraph 5, the product length of pBAV950 increased to 1456 base pairs (bp) from the BAV-3 wild type length of 1393 bp as measured by PCR. As described in the Tikoo Declaration, a rabbit polyclonal anti-sera to BAV-3 pIX recognized a 16 kDa protein in pBAV950 and a 14 kDa protein of wild type BAV-3. The sequence of the pBAV950 modified capsid pIX gene shown in the Tikoo Declaration, Exhibit 5, confirms the presence of an RGD peptide.

As described in Tikoo Declaration, paragraph 6, BAV950 exhibited altered tropism and was able to transduce human cell lines HeLa and A549. Ten fold more viral DNA was found in the BAV950 infected human HeLa and A549 cells, as compared to HeLa and A549 cells infected with wild type BAV-3. The results demonstrate that pBAV950, having a modified capsid pIX gene comprising nucleic acid encoding an RGD peptide, exhibits modified tropism for human

cells. Thus, a bovine adenovirus vector comprising a modification in a polynucleotide encoding a capsid pIX protein is associated with altered tropism.

The Examiner rejects the claims alleging that the specification does not reasonably provide enablement for any species other than an illustrative embodiment, yet the Examiner has not provided any technical evidence or reasonable explanation to support her rejection. Applicants have demonstrated that by modifying two different bovine capsid proteins associated with tropism, that is the bovine capsid fiber protein and bovine capsid pIX protein, species tropism is altered. The present invention also encompasses adenovirus capsid proteins modified to contain peptide sequences that allow the virus to recognize alternative host cells. See the specification at page 30, lines 19-22. The present invention also encompasses bovine adenovirus comprising the replacement of one bovine serotype adenovirus capsid protein with another bovine serotype adenovirus capsid protein in order to modify bovine cell-type tropism. See the specification at page 23, lines 25-28.

The Examiner states at page 3 of the Office Action that the claims are evaluated for scope of enablement based on the Wands analysis, and that such an analysis does not need to be specifically enumerated. The law regarding enablement of invention is clear. The test of enablement is whether one reasonably skilled in the art could make and use the invention from the disclosures in the patent application coupled with information known in the art without undue experimentation. Applicants submit that no undue experimentation is necessary to practice the invention across its full scope.

Regarding the quantity of experimentation necessary, the courts have clearly taught that a considerably amount of experimentation is permissible, if it is merely routine. Claim 1 recites "A bovine adenovirus vector comprising a modification in a polynucleotide encoding a capsid protein, or fragment thereof, wherein said capsid protein, or fragment thereof, is associated with tropism and wherein said modification is associated with altered tropism." Claim 35 recites "A recombinant bovine adenovirus comprising a modification in a polynucleotide encoding a capsid

protein, or fragment thereof, wherein said capsid protein, or fragment thereof, is associated with tropism and wherein said modification is associated with altered tropism."

Mammalian capsid proteins were known in the art at the time of the filing of the present application. See for example Fields Virology, supra. Mammalian capsid proteins are also disclosed in the specification. See the specification at page 24, lines 14-19 which describe capsid regions of BAV3; Figure 2 which provides the transcriptional map of BAV-3; Figures 12-16 which depict the amino acid sequences for mammalian adenovirus fiber proteins; and page 25, lines 3-13 which disclose mammalian capsid proteins, including ovine, porcine and canine fiber proteins. Additional bovine adenovirus capsid proteins were known in the art at the time of the filing of the present patent application. See for example, Reddy et al. 1998, supra. Bovine adenovirus vectors comprising a modification in a polynucleotide encoding a capsid protein are prepared using standard molecular biology techniques and by using methods disclosed in the specification. For example, see the specification at page 25, line 14 through page 28, line 20. Assaying for modifications in tropism can be performed in accordance with techniques known in the art and according to procedures taught in the specification. See for example, the specification at page 42, Example 3. Regarding the amount of direction or guidance provided, methods for constructing bovine adenovirus vectors comprising a modification in a polynucleotide encoding a capsid protein, or fragment thereof, are known in the art and provided in the specification. Mammalian adenovirus capsid proteins are known by those of skill in the art and are provided in the specification. Methods for assaying for modification in tropism are known by those of skill in the art and are provided in the specification. No undue experimentation is necessary to practice the invention across its full scope.

Regarding the presence or absence of working examples, Section 112, first paragraph does not require any working examples to be present in the specification. Second, the specification provides enabling disclosure for the claimed invention. It is irrelevant whether a disclosure of how to make and use the invention is provided through broad teachings or illustrative examples. Nonetheless, the present specification does provide working examples of

the present invention. Example 1 provides construction of BAV600, a BAV3 vector comprising nucleic acid encoding the HAV-5 fiber knob fused to the BAV-3 tail and shaft, an illustrative embodiment encompassed within the present invention. Example 2 provides characterization of BAV600. Example 3 provides disclosure on transduction of human cell lines by BAV600. Additional disclosure is provided in Examples 4 through 7 that validates the modified tropism of BAV600 for human cells. Given the guidance in the specification and the knowledge in the art, one skilled in the art would be able to make and use addition embodiments encompassed with the present invention without resorting to undue experimentation. No undue experimentation is necessary to practice the invention across its full scope. In view of the arguments and evidence presented, Applicants respectfully request withdrawal of this Section 112, first paragraph rejection of claims.

B. The Examiner states that the specification teaches the insertion of a heterologous fiber protein into the bovine adenovirus to alter the viral tropism. Claim 1 recites "A bovine adenovirus vector comprising a modification in a polynucleotide encoding a capsid protein, or fragment thereof, wherein said capsid protein, or fragment thereof, is associated with tropism and wherein said modification is associated with altered tropism" and claim 35 recites "A recombinant bovine adenovirus comprising a modification in a polynucleotide encoding a capsid protein, or fragment thereof, wherein said capsid protein, or fragment thereof, is associated with tropism and wherein said modification is associated with altered tropism."

Applicants have elected fiber for prosecution, with traverse. The present invention encompasses a bovine adenovirus vector wherein the capsid protein, or fragment thereof, is replaced with a polynucleotide encoding a heterologous mammalian capsid protein. See for example, the specification at page 6, lines 1-7. Capsid proteins are known in the art, are disclosed herein and include penton, hexon and fiber proteins as well as IIIa, VI, VIII and IX proteins. The present invention encompasses other embodiments, such as adenovirus capsid proteins modified to contain peptide sequences that allow the virus to recognize alternative host cells and bovine adenovirus comprising the replacement of one bovine serotype adenovirus

capsid protein with another bovine serotype adenovirus capsid protein in order to modify bovine cell-type tropism.

The present specification demonstrates that in an illustrative embodiment, a bovine adenovirus capsid fiber protein knob region replaced with a human fiber protein knob region results in modified tropism of the bovine adenovirus for human cells. The Tikoo Declaration discloses that transduction of human cells is achieved with a BAV comprising a modified adenovirus capsid pIX gene.

The Examiner at page 4 of the Office Action alleges that in order to achieve viral entry of a recombinant virus, more than just the fiber protein may need to be mutated, yet Applicants demonstrate in the specification that transduction of human cells is achieved with a bovine adenovirus containing a human fiber region.

The Examiner references Krasnykh et al. (1996, *J. of Virol.* vol. 70:6839) and concludes that recombinant fiber binding its receptor does not trigger internalization and that the association of the recombinant fiber with recombinant penton base does trigger internalization. Applicants point out that the claims do not recite triggering internalization.

The Examiner references Reddy et al. (1999, *J. Virol.* 73:9137) and alleges that Reddy et al. indicate that more than the fiber protein is needed to introduce the bovine adenovirus construct into a human cell line. The Examiner suggests that introduction of an RGD motif may facilitate the entry of virus into cells. Applicants demonstrate that that transduction of human cells is achieved with a bovine adenovirus comprising a human fiber region in the absence of RGD.

The Examiner contradicts the teachings of the specification and has not provided any evidence to support her allegations of non-enablement.

The Examiner alleges that the specification does not teach altering the hexon or penton base only in order to facilitate entry of virus into a non-bovine cell. First, Applicants point out that the claims do not recite altering the hexon or penton base only. Secondly, the Examiner provides no evidence to support her rejection of claims. Applicants submit that one of skill in

the art would be able to make and use the claimed invention without resorting to undue experimentation.

In view of the arguments and evidence presented, Applicants respectfully request withdrawal of the Section 112, first paragraph rejection of claims.

Concerning rejection of claims under 35 U.S.C. § 103(a)

A. Claims 1, 2, 5, 6, 9-11, 14-17, 21, 22, 27, 28, 35, 41, 42, 43, 46-49 and 51 stand rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Mittal et al. (U.S. Pat. No. 5,820,868, 1998, see IDS Paper No. 3), Krasnykh et al. (Journal of Virology, 1996, see IDS Paper No. 3) and Reddy et al. (Journal of Virology, 199, see IDS Paper No. 3).

Applicants traverse this rejection of claims. Applicants do not agree or concede that a *prima facie* case of obviousness has been established and submit that the invention is non-obvious in view of the cited references. In order to establish a *prima facie* case of obviousness, there has to be, *inter alia*, some motivation or suggestion provided by the references, or in combination with the knowledge available to the skilled artisan, to modify the art cited or to combine reference teachings. Applicants submit that there is no motivation to combine references.

At page 6 of the Office Action, the Examiner characterizes the invention as the fiber protein is replaced with a heterologous fiber protein. Applicants point out that this is one embodiment encompassed within the invention.

The Examiner cites Mittal et al. and concludes that Mittal et al. do not teach inserting a heterologous sequence into the fiber region or modifying the fiber region of a bovine adenovirus in order to alter the tropism of the virus. The Examiner cites Krasnykh et al. and concludes that Krasnykh et al. do not teach modifying tropism of a bovine adenovirus. The Examiner cites Reddy et al. and concludes that Reddy et al. direct using BAV-3 as a viral vector for therapy in humans. The Examiner states that Reddy et al. disclose that transfer vectors with a high transduction efficiency are needed for therapy in humans and that a strategy is to replace the knob region of the BAV-3 fiber with that of HAV. The Examiner states that this is possible, as

the entry of ovine adenovirus into human cells was enhanced when the knob region of the fiber was replaced with that of HAV-5. The Examiner states that Reddy et al. teach introduction of an RGD motif to facilitate entry into human cells.

First of all, Applicants submit that there is no motivation provided to combine references. There is no suggestion to combine Mittal et al, which the Examiner states do not teach altering tropism of the virus by modifying the fiber region, with Krasnykh et al., which the Examiner states do not teach modifying tropism of a bovine adenovirus, with Reddy et al., which generally discuss replication-defective BAV-3 as an expression vector.

Regarding Reddy et al., the Examiner concludes that Reddy et al. teach producing a bovine adenovirus with altered tropism to infect human cells. Reddy et al. do not specifically teach how to make a bovine adenovirus with altered tropism and do not provide a reasonable expectation that the presently claimed invention will succeed. An obviousness rejection can not be based on what a person of skill might try; both the suggestion and the expectation of success must be found in the cited reference, not Applicants' disclosure. Reddy et al. at best represents an invitation to experiment based on utilizing an RGD motif. Applicants demonstrate that the transduction of human cells is achieved with a bovine adenovirus comprising a human fiber in the absence of RGD. Reddy et al. do not provide an expectation that the presently claimed invention will succeed. Reddy et al. reference Xu et al. (1998, *Virology*, 248:62-71) as disclosing an ovine adenovirus system. Xu et al. have no teachings or suggestions of bovine adenovirus and do not provide a reasonable expectation that the claimed invention will succeed.

Furthermore, in determining obviousness, Section 103 expressly requires considering the claimed invention "as a whole". The properties and advantages of the invention are part of the invention as a whole. As described in the Tikoo Declaration at paragraphs 8-10, a bovine adenovirus that comprises nucleic acid encoding a HAV-5 fiber knob region fused to the BAV-3 tail and shaft is unexpectedly able to transduce non-human mammalian cell lines. As disclosed in the Tikoo Declaration at paragraph 9, following methods for transduction disclosed in the present specification at page 42, Example 3, BAV600 was used to transduce swine testes cells

(ST), Madin Darby canine kidney cells (MDCK), Crandell Ress kidney feline cells (CRKF), and African green monkey kidney cells (VERO). The cells were grown in T25 flasks and infected with BAV600 at a Multiplicity of Infection (m.o.i) of 5. Forty eight hours after infection, the percentage of GFP-fluorescence positive cells were determined by flow cytometry. The results show that BAV600 was able to transduce porcine cells, canine cells, feline cells and green monkey cells at a significantly higher level than a control bovine adenovirus lacking the human fiber knob region.

This unexpected property of a bovine adenovirus vector comprising a human fiber region, an illustrative embodiment encompassed within the present invention, is not taught, suggested or appreciated by any of the references cited by the Examiner, taken alone or in combination.

Applicants submit that there is no motivation to combine the references cited by the Examiner. As concluded by the Examiner, Mittal et al. do not teach altering tropism of the virus by modifying the fiber region and Krasnykh et al. do not teach modifying tropism of a bovine adenovirus. Reddy et al. do not specifically teach the production of a bovine adenovirus having altered tropism and do not provide an expectation that the presently claimed invention will succeed.

Furthermore, the unexpected property that a bovine adenovirus vector comprising a human knob gene region is able to transduce non-human mammalian cells is not taught suggested or appreciated by any of the cited references.

Therefore, Applicants submit that when the invention is viewed as a whole, this obviousness rejection must fail as a matter of law. Applicant request withdrawal of this Section 103 rejection of claims.

B. Claims 1, 2, 5, 6, 9-17, 21, 22, 27, 28, 35, 41, 42, 43 and 46-51 stand rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Romanczuk et al. (WO 99/36545, see IDS Paper No. 3) and Reddy et al. (Journal of Virology, 1999, see IDS Paper No. 3).

Applicants traverse this rejection of claims.

The Examiner cites Romanczuk et al. as teaching the production of chimeric adenovirus vector by modifying the capsid protein, yet the Examiner concludes that the reference utilizes human adenovirus and that there are no teachings in Romanczuk et al. regarding a bovine adenovirus. The Examiner applies Reddy et al. and concludes that Reddy et al. directs using BAV-3 as a viral vector for human use, concludes that introduction of an RGD motif will facilitate entry of BAV into human cells and further concludes that Reddy et al. do not teach using bovine adenovirus vector type 1 or type 2.

There is no motivation provided for combining Romanczuk et al. which has no teachings regarding bovine adenovirus, with Reddy et al. Furthermore, the claimed invention, when taken as a whole, is not rendered obvious by the combination of Romanczuk et al. and Reddy et al.

Romanczuk et al. generally relate to adenovirus vectors having modified capsid proteins which comprise heterologous ligands. See the Romanczuk et al. abstract. Romanczuk et al., have no teachings about bovine adenovirus, much less bovine adenovirus comprising a modification in a polynucleotide encoding a capsid protein. As discussed above, Reddy et al. do not provide an expectation that the presently claimed invention will succeed. Neither reference has any teachings, suggestions or appreciation of the fact that a bovine adenovirus vector comprising a human fiber protein would be able to transduce non-human mammalian cells as disclosed in the Tikoo Declaration.

The Examiner at page 10 of the Office Action states that "one having ordinary skill in the art would have been motivated to utilize a bovine adenovirus as a vaccine vector because the average human population would not have produced neutralizing antibodies to bovine adenovirus as this virus would not normally infect the population", yet the Examiner does not provide any evidence or citation to support this allegation. The Examiner also alleges that utilizing a bovine adenovirus vector as a vaccine vector would reduce the risk of recombination with wild type viral sequences creating a replication competent virus. The Examiner does not provide any evidence or citation to support this allegation. The Examiner alleges that utilizing BAV type 1 and 2 would allow for multiple vaccination with a bovine adenovirus vector as the

subject would not have made neutralizing antibodies to the particular vectors, yet the Examiner concludes that Romanczuk et al. have no teachings regarding a bovine adenovirus and concludes that Reddy et al. do not teach using bovine adenovirus vector type 1 or type 2. The Examiner does not provide any evidence or citation to support the allegations. In order to support an obviousness rejection, the teachings or suggestions, as well as the expectation of success, must come from the art cited and not Applicants' disclosure. General conclusions concerning what is "basic knowledge" or "common sense" to one of ordinary skill in the art without specific factual findings and concrete evidence in the record to support these findings will not support an obviousness rejection. See In re Lee, 277 F.3d 1338, 1345 61 USPQ 2d 1430, 1434-35 (Fed. Cir. 2002).

Applicants submit that the Examiner has not met her burden of making a *prima facie* case of obviousness. Furthermore, when taken as a whole, the presently claimed invention is not rendered obvious by the combination of art cited by the Examiner. In view of the evidence and arguments of record, Applicants respectfully request withdrawal of the Section 103 rejections of claims.

CONCLUSION

Applicants have made a sincere effort to overcome the rejections and address all issues that were raised in the outstanding Office Action. Accordingly, reconsideration and allowance of the pending claims are respectfully requested. If it is determined that a telephone conversation would expedite the prosecution of this application, the Examiner is invited to telephone the undersigned at the number given below.

In the unlikely event that the transmittal letter is separated from this document and the Patent Office determines that an extension and/or other relief is required, Applicants petition for any required relief including extensions of time and authorizes the Assistant Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to **Deposit Account No. 03-1952** referencing docket no. 293102003000.

Respectfully submitted,

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the Claims:

Claims 23 and 24 have been amended, as follows:

23. (Amended) The adenovirus vector of claim 22 wherein said polynucleotide encoding said heterologous protein is inserted in the adenovirus E1 gene region.

24. (Amended) The adenovirus vector of claim 22 wherein said polynucleotide encoding said heterologous protein is inserted in the adenovirus E3 gene region.